Pharmacokinetic and tolerability of iOWH032, an inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel, in normal volunteers and cholera patients

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Key funder: Bill & Melinda Gates Foundation

Introduction

iOWH032 is a novel, low-molecular weight compound being developed as an anti-secretory agent for the treatment of cholera toxin–induced secretory diarrhea, acting via inhibition of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel. The safety of iOWH032 in normal volunteers and subjects with cholera is critical to determine the potential for future development of this compound. The purpose of the current study was to evaluate the pharmacokinetics, tolerability, and bioequivalence of iOWH032 in normal volunteers and in cholera patients with severe diarrhea.

Methods

Pharmacokinetic Analysis

• The plasma profile of iOWH032 from each subject was evaluated using a non-compartmental pharmacokinetic approach with WinNonlin® (v. 5.2.1, Pharsight Corp.).

Conclusions

As the Tmax was similar for the two populations, the rate of absorption is probably unaffected, so the reduced absorption in the iOWH032 group is likely due to the reduced and variable transit through the gastrointestinal tract of the patients with severe diarrhea.

• Pharmacokinetics of orally administered iOWH032 showed no ethnic differences between populations of healthy volunteers from the US and Bangladesh, but did show a pronounced reduction in the variability of exposure (Cmax and AUC∞) for the Bangladeshi cholera patients with severe diarrhea.

• The Tmax of 3.8 ± 1.6 h for cholera patients and 4.8 ± 2.6 h for healthy volunteers averaging 3.8 to 4.8 hours (median 3 to 4 hours with a range of 3 to 12 hours).

• The Cmax was similar between the US (1,380 ± 539 ng/mL) and Bangladeshi (1,280 ± 491 ng/mL) healthy volunteers.

• The Cmax and AUC∞ of between 2,700 ± 1,000 ng/mL and 22,700 ± 10,400 ng·h/mL, respectively, compared to those of healthy volunteers (1,280 ± 491 ng/mL and 22,700 ± 10,400 ng·h/mL).

• Patients with severe diarrhea are unlikely to be subject to unexpected high exposures of iOWH032 that could cause unwanted side effects.

• The terminal half-life was determined from a linear regression of the log of the plasma level versus time.

• After addition of [2H5]-iOWH032 as the internal standard, the analytes of interest were separated by HPLC using a C18 reverse-phase column and isocratic elution.